Review Article **ISSN 2639-944X**

Journal of Medical - Clinical Research & Reviews

Mental and Physiological Structures and Mechanisms of Overprotection in the Aetiology of Autoimmune Disease

Anna Cristal-Lilov, Anat Ben Salmon and Ofer Erez*

ROTeM - Center for Practical Professional Training; Clalit Health Services, Israel.

***Correspondence:**
Ofer Erez, ROTeM- Center for Practical Professional Training, Israel, Tel: 972-503376546.

Received: 05 September 2021; **Accepted:** 09 October 2021

Citation: Cristal-Lilov A, Ben Salmon A, Erez O. Mental and Physiological Structures and Mechanisms of Overprotection in the Aetiology of Autoimmune Disease. J Med - Clin Res & Rev. 2021; 5(8): 1-14.

ABSTRACT

Despite the prevalence of autoimmune diseases, and the variety of proposed factors involved in their aetiology, the exact cause of autoimmune disorders is still unknown [1]. As psychotherapist specializing in work with parents for the last sixteen years, and a physician who has worked with adolescents for seventeen years, in this presentation, we propose to consider the analogy between the dynamics of the overprotective family and those of the overactive immune system in autoimmune disorders, and that they are both manifestations of the structures and mechanisms of narcissistic anxiety.

The overprotective parenting style is characterised by parents who present guarding behaviour that is excessive considering the child's developmental stage and the actual risk level in their environment. Overprotective parents tend to obsess over their children's physical and emotional safety, at a level that exceeds the actual level of risk [2]. The impact of overprotective family dynamics upon the emotional development of a child has been extensively discussed [3]. Analogous to this, autoimmune diseases are clinical manifestations of aberrant and "hyper-reactive" autoimmune responses to self-antigens of normal bodily constituents leading to inflammation, cell injury, or a functional disturbance [1]. Medical literature has suggested the correlation between emotional disorders and a variety of autoimmune diseases [4].

This presentation suggests to consider the possibility that high levels of anxiety underlie both overprotective manifestations. Instead of functioning as defence mechanisms aimed to protect the self, they are diverted into a direct attack on it.

Keywords

Autoimmune diseases and disorders, Overprotective Parenting Style, Self-antigens, Autoantibodies, Self-reactive lymphocytes, Child Development, Narcissistic Anxiety.

Introduction

Today, after more than 150 years of research in psychology, we know that parenting behavior towards the child and the parent's behavior in the relationship between themselves, as well as the environment in which the child develops, have the most significant influence upon the child's mental and social wellbeing. The consequences for the emotional and physical wellbeing of adolescents and adults who have experienced neglect, abuse or trauma during childhood has been widely investigated and reported. Many authors such as Anda et al. [5], Felitti et al., [6]; and Heim and, Nemeroff [7] have shown that abuse in childhood is a risk factor for depression, posttraumatic stress disorder, idiopathic chronic pain disorders, substance abuse, antisocial behavior, as well as obesity, diabetes, and cardiovascular disease [5-7].

However, our study focuses on a parenting style which is located on the opposite extreme of a spectrum of styles, one that is based upon parental anxiety and is expressed as overprotection of the offspring. Although some research has explored the impact of overprotective parenting on the emotional well-being of the offspring in later life [8,9] sparse research has been done to investigate the impact of this parenting style on the physical health of our offspring. As psychotherapists and a physician who have

worked with parents, children and adolescents for many years, the hypothesis that induced us to conduct this study was that the overprotective parenting style could also have a significant negative impact on the physical wellbeing of the offspring in later life. We investigated a hypothetical analogy between parenting and the immune system, both of which are intended to protect us from a variety of physical and biological insults and to preserve our health and wellbeing. However, unintentional misuse or dysregulation of both, can lead to unexpected detrimental outcomes. Examining literature in psychology, we consider the effect of parental anxiety and an overprotective parenting style on the emotional equilibrium of the child. Growing up in such an environment causes anxiety in the child, leading to a state of stress which in turn has a significant impact on the developing immune system of the child. This anxiety and resulting immune dysregulation persist into adulthood.

According to Pisetsky [1] autoimmune diseases are clinical manifestations of aberrant and "hyper-reactive" autoimmune responses to self-antigens of normal bodily constituents leading to inflammation, cell injury, or a functional disturbance. Despite the prevalence of autoimmune diseases, the exact etiology of most of the disorders remains unknown [1]. While our knowledge of the mechanisms involved in their symptomatology has grown, it remains unclear who is prone to these disorders and why the presentation and severity differ in each case. We discuss how stress and emotional influences have been implicated in the etiology and are known to cause exacerbation of the disorders [10] and the proposed mechanism through which this occurs which has not yet been thoroughly elucidated.

We present a series of articles which demonstrate the connection between the way individuals cope with stress and the development of immune disorders. The multidisciplinary nature of this paper involves both qualitative and empirical research findings. Therefore, this investigation was conducted in accordance with the premises of Critical Realism which facilitates examination of phenomena in both domains, the connection between them and the understandings that arise from the observations. Through this presentation of a sequential review of literature in psychology, physiology, immunology and medicine we suggest grounding for our hypothesis that overprotective parenting style and an overactive immune system, (which underlies autoimmune and inflammatory diseases), are determined by the same structure and mechanism of narcissistic anxiety.

Becoming a parent presents the individual with a unique set of challenges. When a child is born, the inevitable dependence of the new-born baby upon his parents and the need to protect him provides the parent with a sense of power and control which is simultaneously accompanied by anxiety. All of the baby's needs are fulfilled almost immediately and unconditionally by his caregivers, and at this young age, he does not perceive himself as a separate entity. These conditions provide the baby with an experience of omnipotence. Parents who cannot contain this stage of development, tend to develop a continuous, internal, anxious need to be in the position of a "saviour", which leads to overprotective parental behavior towards their child. Parental narcissistic anxiety develops whenever the parent's position of saviour is undermined. We will present our hypothesis regarding the reasons for the development of the overprotective parenting style in a forthcoming article concerning parenting styles, the impact they have on children and what constitutes "good enough parenting". The starting point of this article is overprotective parents and the emotional and then physical impact of this on the offspring.

The parenting style is the main factor which influences the nature and quality of the child's development, affecting his psychological and social functioning. According to Hoghughi and Speigh [11], apart from the basic requirements of children from their parents of physical care, nutrition, and protection, parents should provide the following emotional needs: (1) love, care, and commitment; (2) consistent limit setting; (3) the facilitation of development. According to Hoghughi and Speigh [11] facilitation of the child's development means enabling him/her to fulfil his/her full potential in every area of functioning, from the physical and intellectual to the spiritual. Since children have a basic need for a secure base from which to explore their environment, "good enough" care involves providing rich and varied stimulation in childhood followed by involvement and support for the child throughout later years until adulthood. Children who experience either under-stimulation or neglect are at risk of educational failure and social handicap in later life [11].

We find this analogous to the immune system which according to Simon, Hollander and McMichael [12] is relatively immature at birth and evolves throughout life as a result of exposure to multiple foreign challenges. Children are continuously exposed to microorganisms, and despite vaccinations, their immune system must overcome viral, bacterial and parasitic infections. Simon, Hollander and McMichael referred to Walker and Slifka and Zinkernagel who stated that the immune reaction facilitates recovery and the stimulation of the antigens results in immunological memory [12-14]. Hayward et al. stated that infections can be documented by symptomatic illnesses suffered by the child or adult, but many infections may be subclinical, but nevertheless induce or boost immune responses [15]. This accumulation of immunological memory is an evolving feature of the adaptive immune response and the protection provided by the immune response, both by antibodies and T cells, is very potent. Most childhood infections happen only once and then protection is lifelong. Through this process, as children grow up, the protection provided by the immune response increases, and young adults suffer fewer infections. [12]. On the other hand, Archie and Tung theorized that when people isolate themselves from one another and spend their time mostly inside, it may reduce "their exposure to richer microbiomes from other sources, thereby limiting the development of our immune system" [16].

In our understanding, overprotective parents are those who show guarding behavior that is excessive considering the child's

developmental stage and the actual risk level in their environment. The need to protect the child from danger, and keep him safe provides the parent with a sense of control and the experience of omnipotence. The unconscious need of the parent to maintain this position may go beyond the child's objective need of protection. This parental tendency may be expressed by encouraging the avoidant approach with the child, which means that the child will be less exposed to stimulating experiences and challenges. Moreover, the parent may also react intensely when the child attempts an activity which the parent wants to prevent him/her from doing, even though it is considered safe at that developmental stage. However, while the parent practices those unconscious needs of his own, by overprotective parenting, he/she actually puts his/her child at risk. Like the immune system analogy, the parents' approach may cause more damage than that which they are allegedly attempting to prevent.

This is supported by Hudson and Rapee [17] who concluded that an association exists between overinvolved parenting and the development of anxiety disorders in children. In their trial, they observed the interaction between mothers and their children during an activity. They found that mothers of children suffering from anxiety-disorders were more involved and more intrusive than mothers of children who did not display anxiety [17]. Tiwari, Podell, Martin, Mychailyszyn, Furr, and Kendall [18] provided a possible explanation for this in that parents of anxious children tend to express experiential avoidance, i.e they are unable or unwilling to tolerate their own internal distress. This leads the parent to behave intrusively in order to reduce the child's distress, and through that, reduce their own internal distress [18]. This aligns with our clinical experience, from which we developed the professional standpoint that children whose parents protect them from any kind of challenge – including challenges faced in education – are at the risk of developing anxiety. This occurs mainly because parental overprotective behavior prevents children from learning, developing and implementing practical coping mechanisms.

Fulton et al., [9] referred to literature in developmental psychology such as that of Kopp, [19] Morris, Silk, Steinberg, Myers, and Robinson, [20] Spinrad et al., [21] which advocates that the way in which parents manage the interaction of their children with the surroundings, and parents' reactions to their children's emotional behavior, demonstrate ways to deal with both internal and external situations, for the child. The researchers concluded when children observe their parents behavior, they construct regulative mechanisms for their emotional reactions to circumstances in their environment. [19-21]. Fulton et al., [9] went on to mention the work of other researchers who related to many factors which are thought to contribute to the development of emotion regulation, including peer interactions [22], traumatic experiences [23], genetics [24], and the child's own temperament or trait vulnerabilities [24]. However she emphasized that Calkins and Hill, related to the early caregiving relationship as being the most crucial context for this process to occur [9,25].

Compas, Connor-Smith, Saltzman, Thomsen, and Wadsworth, stated that based on repeated learning experiences within the early caregiving relationship, children develop different kinds of regulatory strategies that can either be active and engaged or avoidant [8]. Fulton et al. [9] stated that parents who demonstrate fearful or negative attitudes in the face of unpleasant emotional states, may teach their children to cope with situations that arise through approaches which avoid the sources of stress and the distress they may arouse. According to Thompson and Calkins [26], an approach in which arousal is regulated by avoiding the origin of negative feelings (and therefore the feelings themselves), prevents children from acquiring capacity to cope with uncertainty, fear and worry. They stated that an avoidant emotion regulation approach puts children at risk of emotional inhibition in the long run [26]. Hayes et al. [27] concluded that exercising avoidance of unwanted internal experiences may initially result in distress reduction, thereby negatively reinforcing these avoidance behaviors. However, the chronic employment of experiential avoidance has paradoxical outcomes, resulting in increased anxiety and dysregulation in the child [27]. Hannesdottir and Ollendick stated that if the avoidant approach is applied consistently throughout childhood and adolescence, negative emotions become increasingly difficult to contain, causing the child and parents more disabling levels of anxiety [28].

The outcomes of Fulton's et al. [9] study suggested that experiential avoidance is the factor which mediates between perceived parental overprotection and anxiety. They concluded that experiential avoidance may be transmitted from parents to children through behavioral modelling. Aligned with this, Tiwari et al. [18] related to the notion that parents model experiential avoidance in the same manner as they model behavioral avoidance. This encourages the use of experiential avoidance methods in the child and contributes to the preservation of children's anxiety over time. Moreover, Tiwari et al. [18] stated that experiential avoidance is thought to be transmitted from parent to child through modelling, which could constitute intergenerational transmission of psychopathology [18].

Reitman and Asseff [29] and later Clarke, Cooper and Creswell found that parents who suffer from anxiety or panic disorder and are often preoccupied with dangers, tend to present overprotective behaviour [2]. Foulton [9] mentioned the work of Chorpita and Barlow; Hastings et al.; Kiel and Buss; Whaley, Pinto, and Sigman, which found a relationship between overprotective parenting and children's avoidance of novel situations or new people that can induce stress [30-33]. From our professional experience, our understanding of the circumstances of parental overprotection is that the parent is convinced that his behaviour is derived from positive concern for the child's safety. However, growing up in this anxious environment, the child experiences this as intrusion of his parents into his activities which he is capable of conducting independently. This aligns with Reeves et al., [34] who discussed experimental research which proposes that elevated parents' sense of responsibility for the consequences of their child's actions leads to an elevation in intrusiveness and over-involved behaviours in parent's interaction with their children [34]. From our professional

experience, in such circumstances, the child also experiences relentless attacks on his capabilities and specifically his ability to cope with dangers and to develop his individuality. This atmosphere of constant emotional assault leads to a state of anxiety and stress in the child. Three researchers support this position: Reeves et al. who stated that anxious parents may experience increased levels of responsibility in general and that the exaggerated sense of parental responsibility promotes anxiogenic parental behaviours [34]. Spada et al. concluded that overprotected children are more prone to worry and anxiety [3]. Moreover, Laurin et al. discussed parental behaviors, specifically controlling ones such as overprotection and intrusiveness, and found them to be one of the strongest predictors of both the development and preservation of child anxiety [35].

Lebowitz, Leckman, Silverman and Feldman [36] related to anxiety disorders that are prevalent throughout the lifetime, but frequently begin in childhood and cause severe mental distress. They described behavioral systems which may contribute to the development of anxiety in children such as vicarious learning, social referencing, modelling of parental anxiety, overly critical or protective parenting styles and aspects of parental reactions to child anxiety. Biological systems may also have an impact on the development of anxiety such as features of the prenatal environment influenced by maternal anxiety, development and functioning of the oxytocinergic system, as well as genetic and epigenetic transmission [36]. Eley, Bolton, O'connor, Perrin, Smith and Plomin's [37] research on twins tried to identify the genetic origins of different kinds of anxiety within families. However, they concluded that a combination of environmental and individual experiences contribute significantly to the heritability of anxiety [37].

Apart from anxiety, overprotective parenting has been found to be associated with the development of other types of mental illness in the offspring. Bayer, Sanson and Hemphill showed that children raised in an overprotective parenting environment are more likely to suffer from depression in adolescence [38]. This was supported by LeMoyne and Buchanan's study which showed the association between parental overprotection and use of prescription medication for depression and recreational consumption of pain medication in college students [39]. Janssens, Oldehinkel and Rosmalen [40] concluded that overprotected adolescents are more likely to develop Functional Somatic Symptoms (FSS). The authors also suggested that pain, fatigue, and gastrointestinal problems are the most prevalent FSS in children and adolescents [40].

Adverse early life experiences and physical and emotional health

On the opposite extreme of the spectrum of childhood experiences, McEwen [41] discussed the effect of adverse early life experiences on both physical and emotional health. He mentioned Barker and Wadhwa, Sandman and Garite who stated that stress during pregnancy is thought to be a factor for preterm birth, and low birth weight of full-term babies [42,43]. According to Power these low birth weight offspring may be at risk of being overweight and suffering from cardiovascular disease in later life [44]. Repetti, Taylor and Seemans' work claimed that childhood experiences in emotionally cold families increase the likelihood of poor mental and physical health later in life [45]. It has been shown that abuse in childhood is a risk factor for mental illness such as depression, posttraumatic stress disorder, substance abuse, antisocial behavior as well as physical illness such as obesity, diabetes, and cardiovascular disease and idiopathic chronic pain disorders, [5-7]. McEwen also mentioned Evan's work which demonstrated that chaos in the home environment contributes to poor self-regulatory behaviors, a sense of helplessness and psychological distress, as well as increased body mass and elevated blood pressure [41,46,47].

From research such as the above, we have learnt about the effect of abuse, neglect and trauma in childhood on the emotional and physical health of the offspring. However, the impact of the experience of an overprotective parenting style on the physical development of the offspring, has rarely been discussed. Nevertheless, in one study King, Ilic, Koelsch and Sarvetnick [48], suggested that overprotection from exposure to microorganisms might cause a depleted and under-stimulated immune system, which leads to autoimmunity. They reached this conclusion following the observation of the injection of a certain strain of mice with bacterial proteins which led to an increase in T cells and as a result prevented the development of autoimmune diabetes. The researchers concluded that lack of exposure to infections may cause the immune system to act upon the host's own tissues [48].

Autoimmune and inflammatory diseases

According to Pisetsky, [1], autoimmune diseases are clinical manifestations of aberrant and "hyper-reactive" autoimmune responses to self-antigens of normal bodily constituents, leading to inflammation, cell injury, or a functional disturbance [1]. Surace and Hedrich [49] refer to Masters, Simon, Aksentijevich and Kastner, who discussed the fact that historically, autoimmune disorders were differentiated from auto inflammatory conditions, but both are characterized by systemic or organ-specific inflammation causing tissue damage [50]. Autoimmune conditions were characterized by the presence and pathophysiological involvement of autoantibodies and/or self-reactive lymphocyte populations. Auto inflammatory disorders were defined by systemic or organ specific inflammation that occurs in the absence of high titer autoantibodies and autoreactive lymphocytes [49,51]. However, Surace and Hedrich [49] refer to Hedrich [51] who claimed that we currently know that the clinical situation is more complex and changes in immunologic factors can occur over the course of a disease. Tissue damage frequently causes the exposure of intracellular and nuclear components to immune cells, and their activation. As a result, autoantibodies are produced as well as self-directed lymphocyte responses [49,51]. Moreover, some disorders such as psoriasis initially show a mixed immunological pattern that drives inflammation.

Surace and Hedrich [49] mentioned McGonagle and McDermott who in order to resolve this confusion, lead them to propose the "inflammatory spectrum" on which systemic autoimmune/inflammatory conditions can be positioned, with monogenic

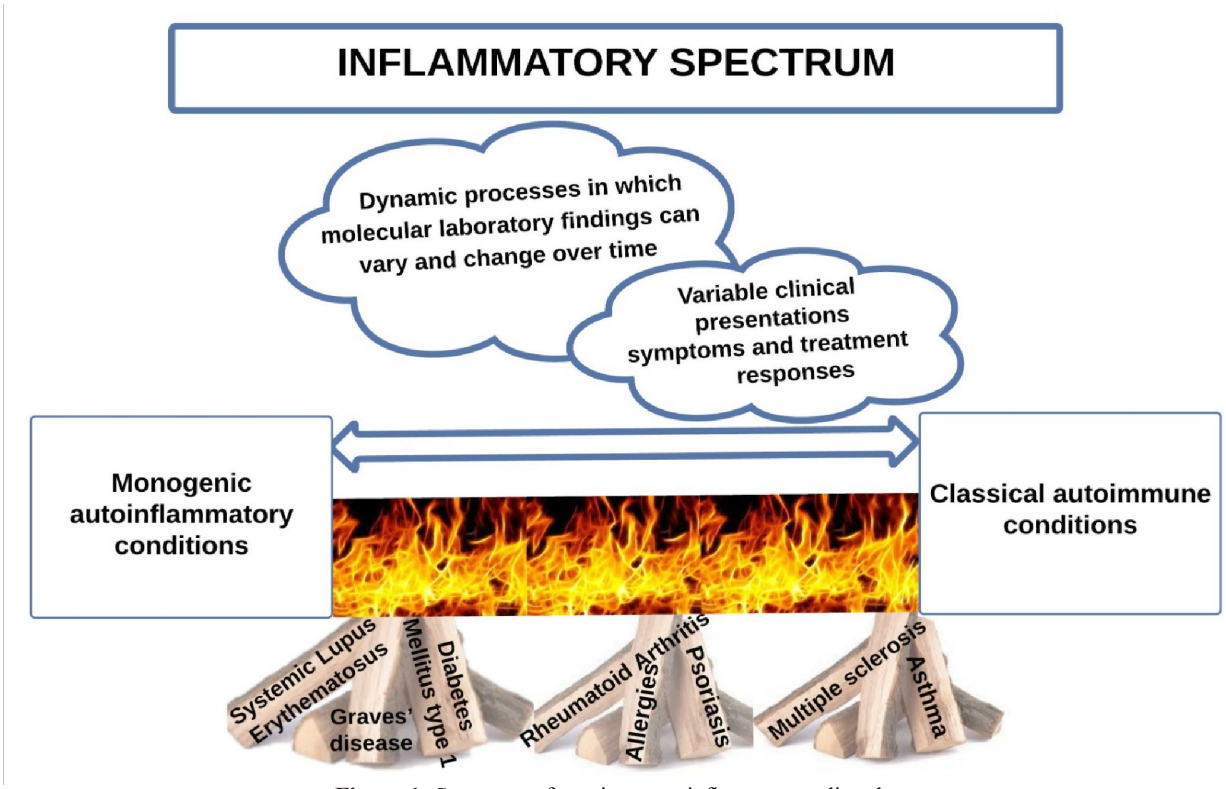

Figure 1: Spectrum of autoimmune-inflammatory disorders.

auto inflammatory conditions at one end and "classical" autoimmune conditions at the other [49,52]. The concept of an inflammatory spectrum also allows us to relate to autoimmune/ inflammatory conditions as dynamic processes in which molecular laboratory findings can change and variable clinical phenotypes, outcomes, and treatment responses can occur [49-51]. For us, the characteristic which is common to all these disorders is the aberrant and overactive activity of the immune system, and in most disorders, the initial cause of this has yet to be elucidated. Like overprotective parents who unintentionally cause harm to their children, the immune system which is meant to protect us from infection and other insults, changes direction and launches an attack on the bodily tissues.

An example of a disorder, whose precise etiology is unknown and which is difficult to classify is Rheumatoid Arthritis (RA). Researchers are currently still unsure if RA is an autoimmune disease and where it should be positioned on the above spectrum. According to Cohen and Fox [53] despite the fact that autoantibodies exist in the condition, it's not certain yet which, if any, of those are critical or essential to RA, or if they are a phenomenon of RA. While in the past therapies for RA were targeted at the cells which invade the synovial fluid like T cells, currently the targets are the cytokines which are involved in the destruction of the tissues, of the joint, specifically Tumor Necrosis Factor (TNF) and Interleukin 1 (IL-1). TNF is the initiator of the pro-inflammatory cytokine cascade in RA, it triggers production of many other cytokines, especially IL-1 and together with IL-1 facilitates activation of T cells. TNF also causes changes in the endothelium (lining of the blood vessels) in the inflamed joint which facilitate the entry of T cells and neutrophils into the tissues. TNF and IL-1 stimulate fibroblasts and macrophages to secrete tissue-destructive enzymes, proteases. Moreover, TNF and IL1 together with osteoclast differentiation factor (ODF) cause the production of osteoclasts (the cells which digest bone) in the joint and in the bone below the joint causing the erosion of bone tissue [53].

Therefore, researchers are currently aware of the invasion of cells into the synovial fluid and the central role of cytokines in RA. However, it still remains unclear as to what causes the excessive production or entry of cytokines into the joints of RA patients.

Interaction between Stress and the immune system

According to Stojanovich and Marisavljevich [54] the etiology of autoimmune disease is considered to be multifactorial involving genetic, environmental, hormonal and immunological factors. Nevertheless, in at least 50% of cases of autoimmune disorders the initiating factors are still unknown. Numerous animal and human studies such as Herrmann Schölmerich and Straub [55] who have shown the impact of stress-inducing events on immune function and the work of Brickman and Shoenfeld [10] who suggested that physical and psychological stress are thought to play a role in the development of autoimmune disease [10,54,55]. Many retrospective studies such as that of Stojanovich found that up to 80% of patients with autoimmune disease reported unusual emotional stress before the outbreak of the disease and other studies suggest that stress can also cause disease exacerbation. Moreover, the disease itself also causes significant stress in the patients, so a vicious cycle of stress and physical illness exists [54,55].

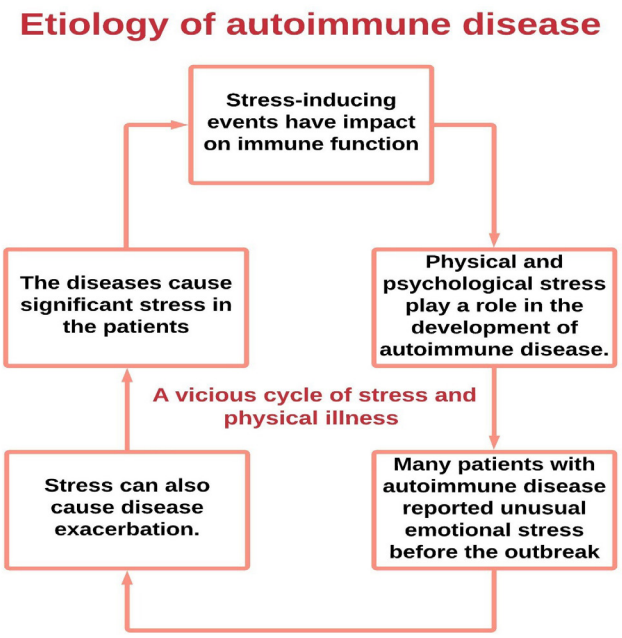

Figure 2: Stress and autoimmune disease.

Research presented above has shown the impact of parental anxiety expressed as an overprotective parenting style, on the psychological well-being and specifically the development of anxiety disorders of the offspring. It is known that anxiety disorders that develop in childhood, persist into adulthood and cause a state of chronic stress. Research has revealed the physiological mechanism through which stress and physical illness interact. In her article Frieri [57] reviewed research papers and review articles which related to the neuro-endocrine-immune (NEI) network in which the proteins and hormones of all those systems interact. Neuroendocrine hormones produced during stress such as epinephrine, norepinephrine, acetylcholine, and substance P, together with the steroid hormone cortisol, may lead to immune dysregulation or altered or amplified cytokine production, resulting in autoimmune diseases or reduced resistance to infection or disease. Glucagon, insulin, growth factors, and numerous other mediators are also involved in these processes [57]. Frieri [57] stated that a dysregulation of the balance of various cytokines due to infection or trauma and the accompanying stress, trigger the activity of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system. Therefore, disorders which are known to be caused by disturbances of immune function are in fact mediated by the NEI network via overproduction of neuropeptides and cytokines. These include allergies, asthma and autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and diabetes mellitus type 1 [57].

Frieri [57] presented knowledge regarding substance P (SP), a neuropeptide, as evidence of the interaction between the systems of the NEI network. SP is produced immediately, in the face of the most noxious and extreme stimuli (stressors), which can potentially compromise biological integrity. According to Baraniuk, Ali, Yuta, Fang and Naranch [58], SP has been shown to have a major role in airway hyper responsiveness and is able to target human skin, airway, nasal epithelium, smooth muscle, and arterioles producing vascular leakage, mucus secretion, bronchoconstriction, mast cell degranulation, and other immunological effects. The work of O'Dorisio et al. discussed SP, vasoactive intestinal peptide (another neuropeptide) and endorphins all which have also been shown to have stimulatory and inhibitory effects on both lymphocytes and macrophages [57-59].

The following additional physiological findings contribute to the understanding of the role of the nervous system in immune disorders:
i) According to Marshall and Agarwal receptors for several stress hormones including corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), cortisol, norepinephrine, and epinephrine are found on lymphocytes and monocytes [60].
ii) Research conducted by Marshall, Agarwal, Lloyd, Cohen, Henninger and Morris [61], demonstrated an increased frequency of viral infections, allergic or asthmatic reaction during examination stress in healthy medical students. This is partially explained by an immune dysfunction related to cytokine dysregulation for IFNγ and IL-10 [61].
iii) Other research conducted by Busse, Kiecolt-Glaser, Coe, Martin, Weiss and Parker [62], has shown that peripheral cytokines can either cross the blood-brain barrier or indirectly influence the production of cytokines within the Central Nervous System (CNS). Direct administration of cytokines into the brain has been shown to alter a variety of neurotransmitter systems, especially the activity of the brain monoaminergic neurons which produce the neurotransmitters dopamine, noradrenaline and serotonin [57,62].

For almost a century, researchers have been searching for the biological etiology of psychiatric illnesses. While anatomical malformations, genetic mutations, epigenetic alterations, and dysfunctional biochemical processes have been considered and some are thought to be correlated with some of those illnesses, no single biological marker has been identified for any of the major psychiatric disorders. Recent research has investigated the presence of inflammatory markers in patients who suffer from psychiatric illnesses and consider if these may be related to the etiology of the disorders:

- Alsheikh and Alsheikh's [63] review demonstrated a significant increase in inflammatory and rheumatic biomarkers in patients with Obsessive Compulsive Disorders (OCD), especially before starting treatment. The most significant inflammatory biomarkers were TNF, interleukins, neutrophil-to-lymphocyte ratio (NLR), and cytokines.
- Spartz, Brown, Farmer, Freeman, Farhadian, Thienemann and Frankovich [64], discussed the utilisation of anti-inflammatory medication for patients suffering from Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) or Pediatric Autoimmune Neuropsychiatric associated with Streptococcal infections (PANDAS). They referred to Swedo, Leckman and Rose [65] and Chang, Frankovich, Cooper stock, Cunningham, Latimer, Murphy, Pasternack Thienemann, Williams, Walter and Swedo, [66], who stated that these disorders are characterized by an abrupt and dramatic onset of obsessive-compulsive (OC) symptoms and/or severely restrictive food intake with at least

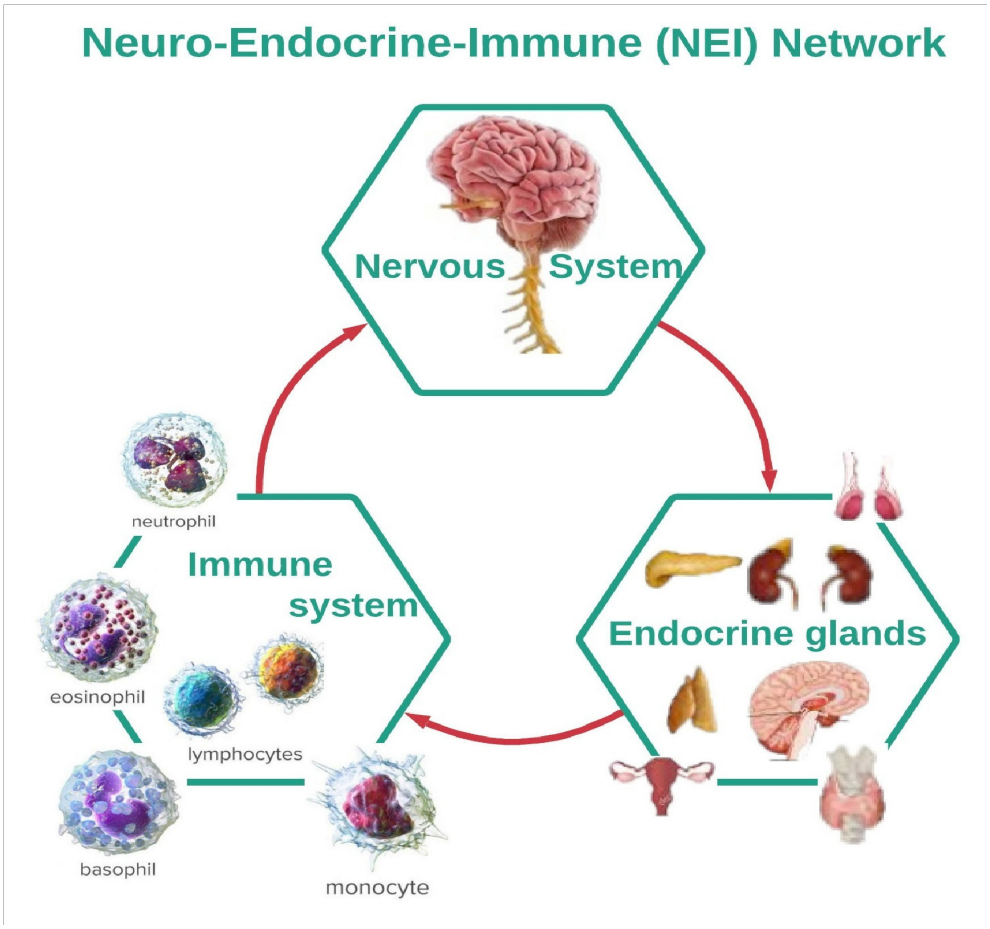

Figure 3: The Neuro-Endocrine-Immune (NEI) network.

two coinciding, equally debilitating symptoms such as anxiety, mood dysregulation, irritability/aggression/oppositionality, behavioral regression, cognitive deterioration, sensory or motor abnormalities, and somatic symptoms [64-66]. Chang et al. [66] stated that when symptom onset is associated with a group A Streptococcus (GAS), the disorder is termed PANDAS. The etiology of PANS is currently unknown, but prior research in humans and animals by Hoffman et al. [67], Yaddanapudi et al. [68], Brimberg et al. [69], Cox et al. [70], Lotan et al. [71], Kumar et al. [72], Macrı et al. [73], Cutforth et al. [74] and Dileepan et al. [75], suggested that the mechanisms underlying PANS/PANDAS involve neuro inflammation and autoimmunity. That research led to trials utilising anti-inflammatory medication as treatment for the disorder, such as that of Spartz et al. which demonstrated improvement in neuropsychiatric symptoms in around one-third of cases [64].

- Marazziti, Muccia and Fontenelle [76] cited a number of other researchers who discussed immune markers which may play a role in the etiology of OCD. They refer to Konuk, Tekın, Ozturk, Atik, Atasoy, Bektas and Erdogan [77] and Sayyah, Boostani, Pakseresht and Malayeri [78] who mentioned the possible role of autoimmune processes expressed by decreased levels of peripheral T–cells that have been related to symptom severity of adult OCD. Nicholson et al., discussed the presence of anti-basal ganglia antibodies in OCD patients. Decreased natural killer (NK) cell activity, increased CD8+ and decreased CD4+ lymphocytes were also described in adult OCD patients by Marazziti, Presta, Pfanner, Gemignani, Rossi, Sbrana, Rocchi, Ambrogi and Cassano and they interpreted these as stress indices [79]. Moreover, Brambilla, Perna, Bellodi, Arancio, Bertani, Perini, Carraro and Gava demonstrated reduced IL-1β levels in adult OCD patients [80], and a trend toward low LPS-stimulated IL-6 levels in OCD patients was reported by Dale [81]. Interestingly, Marazziti et al [79] demonstrated that immune cell alterations seem to normalize after successful treatment with different SSRIs in adult OCD patients.
- Marazziti, Muccia and Fontenelle [76] referred to their previous work Marazziti, Consoli, Baroni and Catena Dell'Osso, [82], and Marazziti, Consoli, Masala, Catena Dell'Osso and Baroni [83], in which the role of the 5-HydroxyTryptophan system in OCD, was related to the immunological alterations of the disorder, pointing to an interaction between the systems. Lestage, Verrier, Palin and Dantzer [84] suggested that two immune modulators, interferon (IFN) γ and α, and TNF-$\boldsymbol{\alpha}$, may activate indoleamine-2,3-dehydrogenase (IDO). This enzyme breaks down tryptophan that is diverted from the production of 5-HT towards the production of kynurenines. The reduction in levels of 5-HT is thought to be correlated with a biochemical susceptibility for the development of psychiatric symptoms or disorders. Moreover, increased kynurenines are thought to have an

excitotoxic effect on the CNS [84].

- Robson, Quinlan and Blakely [85] also recognized that the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) which is known to contribute to the regulation of mood and anxiety (and is strongly related to major depression), has also been to play a role in the modulation of several key aspects of immune system functioning. Peripheral immune activation results in changes in the function and/or expression of many components of 5-HT signalling that are associated with depressive-like symptoms. The author hypothesized that this immune activation may contribute to the development of Major Depression [85].
- Examining Immune data of patients who had experienced an earthquake disaster, Wang et al. showed that patients who suffered from Post-Traumatic Stress Disorder (PTSD) had higher levels of inflammatory cytokine scores, compared to controls who experienced the earthquake but did not suffer from PTSD. They concluded that here is an increase of inflammatory activity in patients suffering from PTSD [86].
- Carta, Loviselli, Hardoy, Massa, Cadeddu, Sardu, Carpiniello, Dell'Osso and Mariotti demonstrated correlation between the presence of thyroid autoimmunity and mood and anxiety disorders [87].
- In a prospective study involving 1.1 million people in Denmark, Anderson showed that depression was associated with a significantly increased risk of autoimmune diseases and may play a role in their etiology [88].

Mechanisms for the effects of Stress on the Immune System

McEwen [41] discussed the protective and damaging effect of the stress mediators. In reaction to acutely stressful experiences, we release chemical mediators, such as catecholamine that increase heart rate and blood pressure. These mediators enable us to function and to react and adapt to the stressful situation. However, chronic elevation of these mediators, causing chronically increased pulse and blood pressure, can cause pathophysiological changes, in the cardiovascular system for example that in the long run can result in strokes and myocardial infarctions. McEwen [41], referred to Sterling and Eyer [89] who in light of the contradictory physiological activities of these mediators which both protect and harm us, introduced the term allostasis. Allostasis literally means “achieving stability through change” and is the active process by which the body responds to daily events and maintains homeostasis [89]. Since chronically increased allostasis can lead to pathophysiology and illness, McEwen [41], proposed the term allostatic load or overload. This refers to the damage to the system caused by either too much stress or from inefficient management of allostasis. During life, when individuals encounter a stressor which they have encountered previously, they should become accustomed to coping with it and moderate their stress response from one occasion to the next. Expressions of allostatic load/overload include not turning off the response efficiently and when it is no longer needed, not turning on an adequate response at the outset, or not habituating to the recurrence of the same stressor and thus ameliorating the allostatic response [41].

McEwen [41] refers to other researchers such as Bierhaus, et al. [90] who stated that apart from the catecholamines, many mediators are involved in allostasis. This includes glucocorticoids which together with the catecholamines regulate pro and anti-inflammatory cytokines. Whereas according to Bierhaus, et al. [90], catecholamines can increase pro inflammatory cytokine production [90], Sapolsky, Romero and Munck, [91] stated that glucocorticoids are known to inhibit this production [91]. However, according to Dinkel, MacPherson and Sapolsky [92] and MacPherson, Dinkel and Sapolsky [93], some exceptions to this exist and the proinflammatory effects of glucocorticoids depend on dose and cell or tissue type [92,93]. Borovikova, Ivanova, Zhang, Yang, Botchkina, Watkins, Wang, Abumrad, Eaton and Tracey, [94] and Thayer and Lane, [95] stated that the parasympathetic nervous system also plays a role in this network of allostasis, and generally opposes the sympathetic nervous system and slows the heart, and also has anti-inflammatory effects [41,94,95]. McEwen [41] suggested that all these mediators interact with each other in a network of regulation which is nonlinear, and the interactions sometimes occur in a biphasic manner. When any one mediator is increased or decreased, there are compensatory changes in the other mediators that depend on the time course and level of change of each of the mediators [41].

Calcagni and Elenkov [96] referred to recent evidence which indicates that the major stress hormones, glucocorticoids and catecholamine (CA), reduce production of IL-12, TNF-$\boldsymbol{\alpha}$ and INF-$\boldsymbol{\gamma}$ by T.helper 1 lymphocytes (Th1) but increase IL-10, IL-4, and TGF-$\boldsymbol{\beta}$ production by T.helper 2 lymphocytes (Th2). Therefore, when the neuroendocrine stress system is activated, an immune and inflammatory response occurs with the induction of a Th2 shift. This may protect the organism from a systemic overshoot immune reaction related to pro inflammatory cytokines produced by Th1 lymphocytes. However, in some specific local responses and under certain conditions, activation of the corticotropin-releasing hormone (CRH)/substance P (SP)-histamine axis, (related to an increase in stress hormones) may induce production of IL-1, IL-6, IL-8, IL-18, TNF-α, and CRP, causing inflammation. Calcagni and Elenkov [96] stated that chronic infections, major depression, atherosclerosis and autoimmune disorders, are characterized by alterations in the balance between the pro vs anti-inflammatory and Th1 vs Th2 cytokines. Therefore, an overactive or sub active stress system, and a dysfunctional neuroendocrine-immune network may involve in the pathogenesis of these diseases, through the development of abnormalities of the “anti-inflammatory feedback" system and/or over activity of the local pro inflammatory factors. In situations of acute or chronic stress, cessation of chronic stress, pregnancy and the postpartum period in which there are significant changes in the activity of the stress system, fluctuations in the local pro/anti-inflammatory and Th1/Th2 cytokine balance, may suppress or potentiate disease activity and influence progression of the disorder [96].

Although cortisol is traditionally considered to be part of the physiologic response to stress, Fries, Hesse, Hellhammer and Hellhammer [99], discussed the low cortisol levels that have been observed in patients with different stress-related disorders such

as chronic fatigue syndrome, fibromyalgia, and post-traumatic stress disorder. These disorders are characterized by a symptom triad of enhanced stress sensitivity, pain, and fatigue. The authors proposed that the phenomenon of hypocortisolism may occur after a prolonged period of hyperactivity of the hypothalamic-pituitary-adrenal axis due to chronic stress as illustrated in an animal model.

Gunnar, and Vazquez [100] also discussed the paradoxical suppression of the Limbic-hypothalamic-pituitary-adrenocortical (LHPA) axis causing hypocortisolism, under conditions of trauma and prolonged stress. They referred to a number of studies that showed that this neuroendocrine axis may be hypo responsive in a number of stress-related states. They hypothesized that adverse conditions that produce elevated cortisol levels early in life may contribute to the development of hypocortisolism in adulthood. However, Gunnar, and Vazquez also mentioned that hypocortisolism also may be a common phenomenon early in human childhood and proposed that developmental studies are required in order to explain the cause of low cortisol and to determine whether the development of hypocortisolism is, in fact, preceded by periods of frequent or chronic activation of the LHPA axis. It is our hypothesis that the experience of an overprotective parenting style may cause a state of chronic stress in the child which persists into adulthood. We propose that cortisol levels should be examined in these cases and compared to those of adults who experienced a good-enough parenting style and those who experienced abuse, trauma or neglect in childhood and suffer from PTSD in adulthood.

In line with this, Heim, Ehlert, and Hellhammer [101] mentioned solid evidence that the adrenal gland is hypoactive in some stress related states. Hypocortisolism has been demonstrated in patients, who suffer from post-traumatic stress disorder (PTSD). However, similar findings have been reported in healthy individuals living under conditions of chronic stress, and also in people suffering from physical disorders, in which stress is thought to play a role in the etiology. This includes such chronic fatigue syndrome, fibromyalgia, other somatoform disorders, rheumatoid arthritis, and asthma. Therefore, Heim, et al emphasized that hypocortisolism seems to be frequent and widespread, but the mechanisms that underlie the phenomenon still need to be elucidated. Moreover, it is unclear whether the mechanism that causes hypocortisolism differs in each of the clinical disorders in which it is present. Mechanisms causing hypocortisolism which have been considered include dysregulations of the HPA axis, on several levels, and genetic vulnerability. It has also been considered that coping and personality styles may affect the development of hypocortisolism. Based on the previous research which they reviewed Heim, et al proposed that a persistent lack of cortisol availability in traumatized or chronically stressed individuals may promote the development of several bodily disorders [101].

Considering the potential cause/reason for changes in HPA axis activity from hyper to hypocortisolism in states of chronic stress, Fries et al. [99] referred to the body's self-adjusting abilities. These abilities counteract the long-term increase in glucocorticoid levels, and protect the organism against their harmful effects, thus contributing to the survival of the organism. Hypocortisolism may develop due to failure of the self-adjusting abilities or 'over-adjustment'. Referring to the work of Hellhammer and Wade, and Heim et al., Fries et al. suggested some possible mechanisms of the 'HPA axis adjustment' (1) the down-regulation of specific receptors on different levels of the HPA axis and its target cells, (2) reduced biosynthesis or depletion of the constituents of the HPA axis at several levels (CRF, ACTH, cortisol) and/or (3) increased negative feedback sensitivity to glucocorticoids.

Stress and Autoimmune Disease

Stojanovich and Marisavljevich [58] mentioned that epidemiological research has shown correlation between traumatic stressors and psychological trauma and the onset of specific diseases such as cardiovascular disease, diabetes, gastrointestinal disease, fibromyalgia, chronic fatigue syndrome, and musculoskeletal disorders. The possible role of psychological stress and of the major stress-related hormones as etiological factors in the pathogenesis of autoimmune disease has been discussed in recent reviews by Herrmann et al. [55]; Wolfe F. [97]; Frieri M. [57]; and Persson et al. [98]. Calcagni and Elenkov [96] referred to several autoimmune diseases including RA, multiple sclerosis (MS), type 1 diabetes mellitus, autoimmune thyroid disease (ATD), and Crohn's disease (CD). In these disorders, a change in the balance between Th1 vs Th2 exists, with an increase in Th1 activity and an excess of IL-12 and TNF-α production and a decrease in Th2 activity and the production of IL-10. The Th1-related autoreactive cellular immune responses which occur in these disorders, are thought to be caused by this shift. It is known that the stress hormone response stimulates the Th2 immune response, leading Calcagni and Elenkov [96] to hypothesise that a hypoactive stress system may cause or maintain the Th1 shift in MS or RA. They mentioned recent studies by; Wilder and Elenkov [104] and Straub and Cutolo [105] that suggest that suboptimal production of cortisol is involved in the onset and/or progression of RA. Calcagni and Elenkov [104] referred to Wilder and Elenkov, according to whom RA is a state of severe, chronic inflammation, characterized by increased production of TNF-α, IL-1, and IL-6. These cytokines are known to stimulate the HPA axis and cortisol production, yet research data suggest that most RA patients have relatively "inappropriately normal" plasma cortisol levels, and that the HPA axis response is suppressed in these patients. It is not yet known whether this is a factor in the cause of the disorder or a result of the disorder [96].

Calcagni and Elenkov [96] referred to studies in humans such as that of Geenen, Godaert, Jacobs, Peters and Bijlsma [102] which showed that patients with RA demonstrated reduced autonomic responses after cognitive tests, suggesting that the SNS does not function appropriately in patients with RA. Calcagni and Elenkov, [96] also mentioned Miller, Jüsten, Schcölmerich and Straub's [103] research which demonstrated a significant reduction of sympathetic nerve fibers in joint tissues of long-term RA patients

which was dependent on the severity of the inflammation. The reduction of sympathetic nerve fibers in the joints of patients with chronic RA may lead to disconnection from the anti-inflammatory input of SNS and the local inflammation becomes autonomous. Moreover, Miller, et al. [103] also found that in RA synovial tissues, primary sensory SP-positive fibers predominate compared to the reduction in sympathetic fibers in a ratio of 10:1. As mentioned above, SP is a powerful pro-inflammatory agent, causing the release of histamine, TNF-α and IL-12, which may lead to the unfavourable pro-inflammatory state, of the disease [96].

More recently the role of epigenetics in autoimmune and inflammatory disorders has been researched. Surace and Hedrich [49] described that epigenetic modifications influence gene expression and alter cellular functions without modifying the genomic sequence. Currently, the pathophysiology of autoimmune/inflammatory diseases is more frequently thought to be a combination of genetic susceptibility and epigenetic modifications arising from exposure to the environment rather than with disease causing gene mutations. Autoimmune/inflammatory diseases are related to complex genetic predispositions and are subject to individual and environmental influences that define individual disease expression or symptomatology and outcomes [49,51]. Surace and Hedrich [49] refer to Hedrich who stated that this is supported by the fact that genetically identical monozygotic twins can differ regarding the frequency of development of autoimmune/inflammatory disorders. These observations resulted in the hypotheses that disease-causing single gene mutations may cause the disorder to develop but do not necessarily define individual outcomes. Disease expression and outcomes are dictated by additional factors, including epigenetics [49].

The literature presented in the first half of this article, grounds the relationship between the experience of overprotective parenting and the development of anxiety in children which persists into adulthood and comprises a chronic state of stress. We have shown that emotional stress causes stimulation of the HPA axis and production of stress hormones, and simultaneous changes in the immune system. However, chronic stress is frequently related to hypocortisolism and as a result dysregulation of the immune system and cytokine production. This represents an important mechanism through which chronic stress affects disease susceptibility, activity, and outcome of various immune-related diseases, which may constitute an epigenetic effect involved in the development of autoimmune disease in later life. Instead of protecting us from infections and other assaults, the immune system attacks specific parts of the body in an analogous way to overprotective parenting which causes damage to the child in a paradoxical manner.

In further research, we will deepen the theoretical grounding of this hypothesis through an inquiry into the reasons for the development of the overprotective parental style and how it is expressed during different stages of life. As practitioners working with children

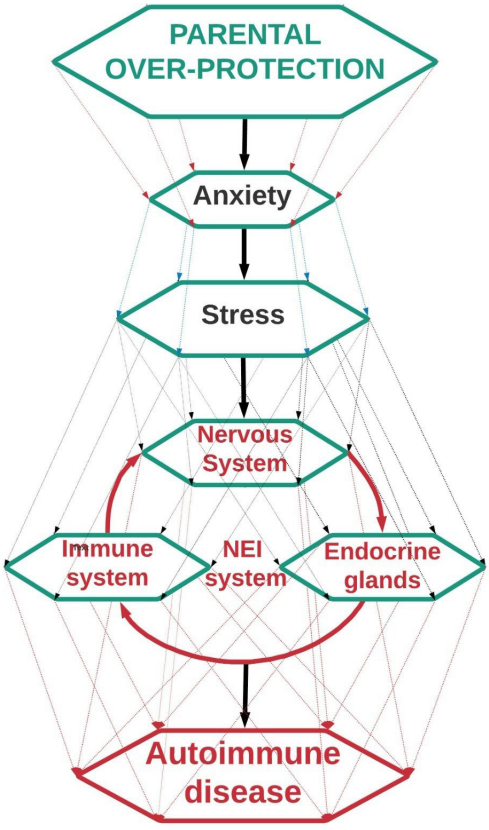

Figure 4: The impact of overprotective parenting on the development of Autoimmune Disease in the offspring.

and their parents, we are primarily concerned with prevention. Therefore, we suggest that these findings will assist parents to comprehend the reasons why modification of their behavior and the achievement of "good enough parenting" is essential for the wellbeing of their children, both emotional and physical.

References

1. Pisetsky DS. Overview of autoimmunity. Uptodate.com. 2020.
2. Clarke K, Cooper P, Creswell C. The Parental Overprotection Scale Associations with child and parental anxiety. Journal of affective disorders. 2013; 151: 618-624.
3. Spada MM, Caselli G, Manfredi C, et al. Parental overprotection and metacognitions as predictors of worry and anxiety. Behavioural and cognitive psychotherapy. 2012; 40: 287.
4. Song H, Fang F, Tomasson G, et al. Association of stress related disorders with subsequent autoimmune disease. Jama. 2018; 319: 2388-2400.
5. Anda RF, Felitti VJ, Bremner JD, et al. The enduring effects of abuse and related adverse experiences in childhood. European archives of psychiatry and clinical neuroscience. 2006; 256: 174-186.
6. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction too many of the leading causes of death in adults The Adverse Childhood Experiences ACE Study. American journal of preventive medicine. 1998; 14: 245-258.
7. Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders preclinical and clinical studies. Biological psychiatry. 2001; 49: 1023-1039.
8. Compas BE, Connor-Smith JK, Saltzman H, et al. coping with stress during childhood and adolescence problems progress and potential in theory and research. Psychological bulletin. 2001; 127: 87.
9. Fulton JJ, Kiel EJ, Tull MT, et al. Associations between perceived parental overprotection experiential avoidance and anxiety. Journal of Experimental Psychopathology. 2014; 5: 200-211.
10. Brickman CM, Shoenfeld Y. The mosaic of autoimmunity. Scandinavian journal of clinical and laboratory investigation. Supplementum. 2001; 235: 3-15.
11. Hoghughi M, Speight ANP. Good enough parenting for all children a strategy for a healthier society. Archives of disease in childhood. 1998; 78: 293-296.
12. Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. Proceedings of the Royal Society B Biological Sciences. 2015; 282: 20143085.
13. Walker JM, Slifka MK. Longevity of T-cell memory following acute viral infection. Memory T Cells. 2010; 96-107.
14. Zinkernagel RM. On immunological memory. Philosophical Transactions of the Royal Society of London. Series B Biological Sciences. 2000; 355: 369-371.
15. Hayward AC, Fragaszy EB, Bermingham A, et al. Comparative community burden and severity of seasonal and pandemic influenza results of the Flu Watch cohort study. The Lancet Respiratory Medicine. 2014; 2: 445-454.
16. Archie EA, Tung J. Social behavior and the microbiome. Current opinion in behavioral sciences. 2015; 6: 28-34.
17. Hudson JL, Rapee RM. Parent-child interactions in clinically anxious children and their siblings. Journal of Clinical Child and Adolescent Psychology. 2002; 31: 548-555.
18. Tiwari S, Podell JC, Martin ED, et al. Experiential avoidance in the parenting of anxious youth Theory research, and future directions. Cognition and emotion. 2008; 22; 480-496.
19. Kopp CB. Regulation of distress and negative emotions A developmental view. Developmental psychology. 1989; 25: 343.
20. Morris AS, Silk JS, Steinberg L, et al. The role of the family context in the development of emotion regulation. Social development. 2007; 16: 361-388.
21. Spinrad TL, Eisenberg N, Gaertner B, et al. Relations of maternal socialization and toddlers' effortful control to children's adjustment and social competence. Developmental psychology. 2007; 43: 1170.
22. Brechwald WA, Prinstein MJ. Beyond homophily a decade of advances in understanding peer influence processes. Journal of Research on Adolescence. 2011; 21: 166-179.
23. Ehring T, Quack D. Emotion regulation difficulties in trauma survivors the role of trauma type and PTSD symptom severity. Behavior therapy. 2010; 41: 587-598.
24. Goldsmith HH, Buss AH, Plomin R, et al. Roundtable what is temperament? Four approaches. Child development. 1987; 505-529.
25. Calkins SD, Hill A. Caregiver influences on emerging emotion regulation. Handbook of emotion regulation. 2007.
26. Thompson RA, Calkins SD. The double-edged sword Emotional regulation for children at risk. Development and psychopathology. 1996; 8: 163-182.
27. Hayes SC, Wilson KW, Gifford EV, et al. Experiential avoidance and behavioral disorders A functional dimensional approach to diagnosis and treatment. Journal of Consulting and Clinical Psychology. 1996; 64: 1152-1168.
28. Hannesdottir DK, Ollendick TH. The role of emotion regulation in the treatment of child anxiety disorders. Clinical Child and Family Psychology Review. 2007; 10: 275-293.
29. Reitman D, Asseff J. Parenting practices and their relation to anxiety in young adulthood. Journal of anxiety disorders. 2010; 24: 565-572.
30. Chorpita BF, Barlow DH. The development of anxiety the role of control in the early environment. Psychological bulletin. 1998; 124: 3.
31. Hastings PD, Sullivan C, McShane KE, et al. Parental socialization vagal regulation and preschoolers' anxious difficulties Direct mothers and moderated fathers. Child

development. 2008; 79: 45-64.

32. Kiel EJ, Buss KA. Maternal accuracy and behavior in anticipating children's responses to novelty Relations to fearful temperament and implications for anxiety development. Social Development. 2010; 19: 304-325.
33. Whaley SE, Pinto A, Sigman M. Characterizing interactions between anxious mothers and their children. Journal of Consulting and Clinical Psychology. 1999; 67: 826-836.
34. Reeves J, Reynolds S, Coker S, et al. An experimental manipulation of responsibility in children a test of the inflated responsibility model of obsessive-compulsive disorder. Journal of Behavior Therapy and Experimental Psychiatry. 2010; 41: 228-233.
35. Laurin JC, Joussemet M, Tremblay RE, et al. Early forms of controlling parenting and the development of childhood anxiety. Journal of Child and Family Studies. 2015; 24: 3279-3292.
36. Lebowitz ER, Leckman JF, Silverman WK, et al. Cross-generational influences on childhood anxiety disorders: pathways and mechanisms. Journal of Neural Transmission. 2016; 123: 1053-1067.
37. Eley TC, Bolton D, O'connor TG, et al. A twin study of anxiety-related behaviours in pre-school children. Journal of Child Psychology and Psychiatry. 2003; 44: 945-960.
38. Bayer JK, Sanson AV, Hemphill SA. Parent influences on early childhood internalizing difficulties. Journal of Applied Developmental Psychology. 2006; 27: 542-559.
39. LeMoyne T, Buchanan T. Does “hovering” matter? Helicopter parenting and its effect on well-being. Sociological Spectrum. 2011; 31: 399-418.
40. Janssens KA, Oldehinkel AJ, Rosmalen JG. Parental overprotection predicts the development of functional somatic symptoms in young adolescents. The Journal of pediatrics. 2009; 154: 918-923.
41. McEwen B. Physiology and neurobiology of stress and adaptation central role of the brain. Physiol Rev. 2007; 87: 873-904.
42. Barker DJ. The fetal origins of coronary heart disease. Acta Paediatrica. 1997; 86: 78-82.
43. Wadhwa PD, Sandman CA, Garite TJ. The neurobiology of stress in human pregnancy implications for prematurity and development of the fetal central nervous system. Progress in brain research. 2001; 133: 131-142.
44. Power C, Li L, Manor O, et al. Combination of low birth weight and high adult body mass index at what age is it established and what are its determinants. Journal of Epidemiology and Community Health. 2003; 57: 969-973.
45. Repetti RL, Taylor SE, Seeman TE. Risky family’s family social environments and the mental and physical health of offspring. Psychological bulletin. 2002; 128: 330.
46. Evans GW. A multi methodological analysis of cumulative risk and allostatic load among rural children. Developmental psychology. 2003; 39: 924.
47. Evans GW, Gonnella C, Marcynyszyn LA, et al. The role of chaos in poverty and children's socioemotional adjustment. Psychological science. 2005; 16: 560-565.
48. King C, Ilic A, Koelsch K, et al. Homeostatic expansion of T cells during immune insufficiency generates autoimmunity. Cell. 2004; 117: 265-277.
49. Surace AEA, Hedrich CM. The role of epigenetics in autoimmune/inflammatory disease. Frontiers in immunology. 2019; 10: 1525.
50. Masters SL, Simon A, Aksentijevich I, et al. Horror auto inflammaticus the molecular pathophysiology of auto inflammatory disease. Annual review of immunology. 2009; 27: 621-668.
51. Hedrich CM. Shaping the spectrum from auto inflammation to autoimmunity. Clinical Immunology. 2016; 165: 21-28.
52. McGonagle D, McDermott MF. A proposed classification of the immunological diseases. PLoS medicine. 2006; 3: e297.
53. Cohen MD, Fox DA. Biologic Therapies for Rheumatoid Arthritis Navigating the Changing Treatment Paradigm. Medscape.org. 2021.
54. Stojanovich L, Marisavljevich D. Stress as a trigger of autoimmune disease. Autoimmunity reviews. 2008; 7: 209-213.
55. Herrmann M, Schölmerich J, Straub RH. Stress and rheumatic diseases. Rheumatic Disease Clinics of North America. 2000; 26: 737-763.
56. Shepshelovich D, Shoenfeld Y. Prediction and prevention of autoimmune diseases additional aspects of the mosaic of autoimmunity. Lupus. 2006; 15: 183-190.
57. Frieri M. Neuroimmunology and inflammation: implications for therapy of allergic and autoimmune diseases. Annals of Allergy Asthma and Immunology. 2003; 90: 34-40.
58. Baraniuk JN, Ali M, Yuta A, et al. Hypertonic saline nasal provocation stimulates nociceptive nerves substance P release and glandular mucous exocytosis in normal humans. American journal of respiratory and critical care medicine. 1999; 160: 655-662.
59. O'dorisio MS, Wood CL, O'dorisio TM. Vasoactive intestinal peptide and neuropeptide modulation of the immune response. Journal of Immunology. 1985; 135: 792s-796s.
60. Marshall GD, Agarwal SK. Stress immune regulation and immunity applications for asthma. In Allergy and asthma proceedings. Ocean Side Publications. 2000; 21: 241.
61. Marshall GD, Agarwal SK, Lloyd C, et al. Cytokine dysregulation associated with exam stress in healthy medical students. Brain behavior and immunity. 1998; 12: 297-307.
62. Busse WW, Kiecolt-Glaser JK, Coe C, et al. NHLBI Workshop summary. Stress and asthma. American journal of respiratory and critical care medicine. 1995; 151: 249-252.
63. Alsheikh AM, Alsheikh MM. Obsessive-Compulsive Disorder With Rheumatological and Inflammatory Diseases A Systematic Review. Cureus. 2021; 13.
64. Spartz, Brown KD, Farmer C, Freeman Jr, et al. Effect of early and prophylactic nonsteroidal anti-inflammatory drugs

on flare duration in pediatric acute-onset neuropsychiatric syndrome an observational study of patients followed by an academic community-based pediatric acute-onset neuropsychiatric syndrome clinic. Journal of child and adolescent psychopharmacology. 2015; 25: 3-13.

65. Swedo SE, Leckman JF, Rose NR. From research subgroup to clinical syndrome modifying the PANDAS criteria to describe PANS pediatric acute-onset neuropsychiatric syndrome. Pediatr Therapeut. 2012; 2: 113.
66. Chang K, Frankovich J, Cooper stock M, et al. From the PANS Collaborative Consortium. Clinical evaluation of youth with pediatric acute-onset neuropsychiatric syndrome PANS recommendations from the 2013 PANS Consensus Conference. Journal of Child and Adolescent Psychopharmacology. 2015; 25: 3-13.
67. Hoffman KL, Hornig M, Yaddanapudi K, et al. A murine model for neuropsychiatric disorders associated with group a β-hemolytic streptococcal infection. Journal of Neuroscience. 2004; 24: 1780-1791.
68. Yaddanapudi K, Hornig M, Serge R, et al. Passive transfer of streptococcus-induced antibodies reproduces behavioral disturbances in a mouse model of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection. Molecular psychiatry. 2010; 15: 712-726.
69. Brimberg L, Benhar I, Mascaro-Blanco, et al. Behavioral pharmacological and immunological abnormalities after streptococcal exposure a novel rat model of Sydenham chorea and related neuropsychiatric disorders. Neuropsychopharmacology. 2012; 37: 2076-2087.
70. Cox CJ, Sharma M, Leckman JF, et al. Brain human monoclonal autoantibody from Sydenham chorea targets dopaminergic neurons in transgenic mice and signals dopamine D2 receptor implications in human disease. The Journal of Immunology. 2013; 191: 5524-5541.
71. Lotan D, Benhar I, Alvarez K, et al. Behavioral and neural effects of intra-striatal infusion of anti-streptococcal antibodies in rats. Brain behavior and immunity. 2014; 38: 249-262.
72. Kumar A, Williams MT, Chugani HT. Evaluation of basal ganglia and thalamic inflammation in children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection and tourette syndrome a positron emission tomographic PET study using 11C-[R]-PK11195. Journal of child neurology. 2015; 30: 749-756.
73. Macrì S, Ceci C, Onori MP, et al. Mice repeatedly exposed to Group-A β-Haemolytic Streptococcus show perseverative behaviors impaired sensorimotor gating and immune activation in rostral diencephalon. Scientific reports, 2015; 5: 1-19.
74. Cutforth T, DeMille MM, Agalliu I, et al. CNS autoimmune disease after Streptococcus pyogenes infections: animal models cellular mechanisms and genetic factors. Future neurology. 2016; 11: 63-76.
75. Dileepan T, Smith ED, Know land D, et al. Group A Streptococcus intranasal infection promotes CNS infiltration by streptococcal-specific Th17 cells. The Journal of clinical investigation. 2016; 126: 303-317.
76. Marazziti D, Mucci F, Fontenelle LF. Immune system and obsessive-compulsive disorder. Psycho neuro endocrinology. 2018; 93: 39-44.
77. Konuk N, Tekın IO, Ozturk U, et al. Plasma levels of tumor necrosis factor-alpha and interleukin-6 in obsessive compulsive disorder. Mediators of inflammation. 2007.
78. Sayyah M, Boostani H, Pakseresht S, et al. A preliminary randomized double–blind clinical trial on the efficacy of celecoxib as an adjunct in the treatment of obsessive-compulsive disorder. Psychiatry research. 2011; 189: 403-406.
79. Marazziti D, Presta S, Pfanner C, et al. Immunological alterations in adult obsessive-compulsive disorder. Biological psychiatry. 1999; 46: 810-814.
80. Brambilla F, Perna G, Bellodi L, et al. Plasma interleukin-1β and tumor necrosis factor concentrations in obsessive–compulsive disorders. Biological psychiatry. 1997; 42: 976-981.
81. Dale RC. Post-streptococcal autoimmune disorders of the central nervous system. Developmental Medicine and Child Neurology. 2005; 47: 785-791.
82. Marazziti D, Consoli G, Baroni S, et al. Past, present and future drugs for the treatment of obsessive-compulsive disorder. Current medicinal chemistry. 2010a; 17: 3410-3421.
83. Marazziti D, Consoli G, Masala I, et al. Latest advancements on serotonin and dopamine transporters in lymphocytes. Mini reviews in medicinal chemistry. 2010b; 10: 32-40.
84. Lestage J, Verrier D, Palin K, et al. The enzyme indoleamine 2,3-dioxygenase is induced in the mouse brain in response to peripheral administration of lipopolysaccharide and superantigen. Brain, behavior, and immunity. 2002; 16: 596-601.
85. Robson MJ, Quinlan MA, Blakely RD. Immune system activation and depression roles of serotonin in the central nervous system and periphery. ACS chemical neuroscience. 2017; 8: 932-942.
86. Wang W, Wang L, Xu H, et al. Characteristics of pro-and anti-inflammatory cytokines alteration in PTSD patients exposed to a deadly earthquake. Journal of affective disorders. 2019; 248: 52-58.
87. Carta MG, Loviselli A, Hardoy MC, et al. The link between thyroid autoimmunity antithyroid peroxidase autoantibodies with anxiety and mood disorders in the community a field of interest for public health in the future. BMC psychiatry. 2004; 4: 1-5.
88. Andersson NW, Gustafsson LN, Okkels N, et al. Depression and the risk of autoimmune disease: a nationally representative prospective longitudinal study. Psychological Medicine. 2015; 45: 3559-3569.
89. Sterling P, Eyer J. Allostasis A New Paradigm to Explain

Arousal Pathology. Handbook of Life Stress Cognition and Health. 1988.

90. Bierhaus A, Wolf J, Andrassy M, et al. A mechanism converting psychosocial stress into mononuclear cell activation. Proceedings of the National Academy of Sciences. 2003; 100: 1920-1925.

91. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses. Integrating permissive suppressive stimulatory and preparative actions. Endocrine reviews. 2000; 21: 55-89.

92. Dinkel K, MacPherson A, Sapolsky RM. Novel glucocorticoid effects on acute inflammation in the CNS. Journal of neurochemistry. 2003; 84: 705-716.

93. MacPherson A, Dinkel K, Sapolsky R. Glucocorticoids worsen excitotoxin-induced expression of pro-inflammatory cytokines in hippocampal cultures. Experimental neurology. 2005; 194: 376-383.

94. Borovikova LV, Ivanova S, Zhang M, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature. 2000; 405: 458-462.

95. Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. Journal of affective disorders. 2000; 61: 201-216.

96. Calcagni E, Elenkov I. Stress system activity innate and T helper cytokines and susceptibility to immune-related diseases. Annals of the New York Academy of Sciences. 2006; 1069: 62-76.

97. Wolfe F. Psychological distress and rheumatic disease editorial review. Scandinavian journal of rheumatology. 1999; 28: 131-136.

98. Persson LO, Berglund K, Sahlberg D. Psychological factors in chronic rheumatic diseases--a review. The case of rheumatoid arthritis current research and some problems. Scandinavian Journal of Rheumatology. 1999; 28: 137-144.

99. Fries E, Hesse J, Hellhammer J, Hellhammer DH. A new view on hypocortisolism. Psychoneuroendocrinology. 2005 Nov 1;30(10):1010-6.

100. Gunnar MR, Vazquez DM. Low cortisol and a flattening of expected daytime rhythm: Potential indices of risk in human development. Development and psychopathology. 2001 Sep;13(3):515-38.

101. Heim C, Ehlert U, Hellhammer DH. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. Psychoneuroendocrinology. 2000 Jan 1;25(1):1-35.

102. Geenen R, Godaert GL, Jacobs JW, Peters ML, Bijlsma JW. Diminished autonomic nervous system responsiveness in rheumatoid arthritis of recent onset. The Journal of rheumatology. 1996 Feb 1;23(2):258-64.

103. Miller LE, Jüsten HP, Schcölmerich J, Straub RH. The loss of sympathetic nerve fibers in the synovial tissue of patients with rheumatoid arthritis is accompanied by increased norepinephrine release from synovial macrophages. The FASEB Journal. 2000 Oct;14(13):2097-107.

104. Wilder RL, Elenkov IJ. Hormonal regulation of tumor necrosis factor-α, interleukin-12 and interleukin-10 production by activated macrophages: a disease-modifying mechanism in rheumatoid arthritis and systemic lupus erythematosus?. Annals of the New York Academy of Sciences. 1999 Jun;876(1):14-31.

105. Straub RH, Cutolo M. Involvement of the hypothalamic--pituitary--adrenal/gonadal axis and the peripheral nervous system in rheumatoid arthritis: viewpoint based on a systemic pathogenetic role. Arthritis and rheumatism. 2001 Mar 1;44(3):493-507.

106. Kiel EJ, Buss KA. Prospective relations among fearful temperament, protective parenting, and social withdrawal: The role of maternal accuracy in a moderated mediation framework. Journal of abnormal child psychology. 2011 Oct;39(7):953-66.

107. Whaley SE, Pinto A, Sigman M. Characterizing interactions between anxious mothers and their children. Journal of consulting and clinical psychology. 1999 Dec;67(6):826.